# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER

0198/00047

U.S. APPLICATION NO. (If known, see 37 C

09/242103

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIM |
|---|---|---|
| PCT/FR98/01241 | 12 June 1998 | 13 June 1997 |

TITLE OF INVENTION

Implant for Subcutaneous or Intradermal Injection

APPLICANT(S) FOR DO/EO/US

Jerome Asius, Hatem Fessi, Franck Gouchet, Benedicte Laglenne and Elisabeth Laugier-Laglenne

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other informat

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. § 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay ex. until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claime. date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern other document(s) or information included:**

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is incl
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter
16. ☒ Other items or information:

    International Search Report. Verification of Translation

| U.S. APPLICATION NO (If known, see 37 CFR 1 5) | INTERNATIONAL APPLICATION NO PCT/FR98/01241 | ATTORNEY'S DOCKET NUMBER, 0198/00047 |
|---|---|---|

| ☒ The following fees are submitted: | CALCULATIONS | PTO U |
|---|---|---|
| **Basic National Fee (37 CFR 1.492(a)(1)-(5)):** Search Report has been prepared by the EPO or JPO . . . . . **$840.00** | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) . . . . . **$670.00** | | |
| No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . . . **$760.00** | | |
| Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO . . . . . **$970.00** | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) . . . . . **$ 96.00** | | |
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | **$840** | |
| Surcharge of **$130** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $ | |

| Claims | Number Filed | Number Extra | Rate | | |
|---|---|---|---|---|---|
| Total Claims | 20 -20 = | 0 | X **$18** | $ | |
| Independent Claims | 1 - 3 = | 0 | X **$78** | $ | |
| Multiple dependent claim(s)(if applicable) | | | + **$260** | $ | |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | $840 | |
| Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28) | | | | $ | |
| **SUBTOTAL =** | | | | $840 | |
| Processing fee of **$130** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | | | | $ | |
| **TOTAL NATIONAL FEE =** | | | | $840 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40** per property + | | | | $ 40 | |
| **TOTAL FEES ENCLOSED =** | | | | $880 | |
| | | | | **Amount to be: refunded** | $ |
| | | | | **charged** | $ |

a. ☒ A check in the amount of $880 to cover the above fees is enclosed.

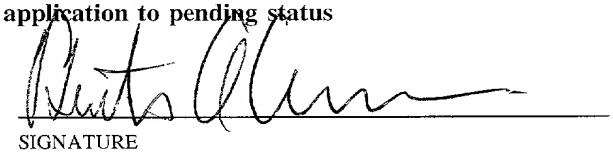
b. ☐ Please charge my Deposit Account No. **22-0185** in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **22-0185**. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revi 1.137(a) or (b) must be filed and granted to restore the application to pending status**

SEND ALL CORRESPONDENCE TO:

**Pollock, Vande Sande & Amernick, R.L.L.P.**
1990 M Street, N.W.
Suite 800
Washington, DC 20036-3425



SIGNATURE

Burton A. Amernick
NAME

24,852
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|---|---|---|
| APPLICANT: | Asius et al | |
| SERIAL NO: | Not assigned | GROUP NO: Not assigned |
| FILING DATE: | Concurrently herewith | EXAMINER: Not assigned |
| FOR: | Implant for Subcutaneous or Intradermal Injection | |

PRELIMINARY AMENDMENT

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-captioned case as follows.

In the Claims:

Please amend the claims as follows.

Claim 3, line 1, delete "either of Claims 1 and 2" and insert ---Claim 1---.

Claim 4, line 1, delete "one of the preceding claims" and insert ---Claim 1---.

Claim 5, line 1, delete "one of the preceding claims" and insert ---Claim 1---.

Claim 6, line 1, delete "one of the preceding claims" and insert ---Claim 1---.

Claim 8, line 1, delete "one of the preceding claims" and insert ---Claim 1---.

Claim 9, line 2, delete "one of the preceding claims" and insert ---Claim 1---.

Please add the following new claims.

10. Implant according to Claim 2, characterized in that the proportion of microspheres or microparticles in the gel is from 50 to 300 g/l, and preferably from 60 t 200 g/l.

11. Implant according to Claim 2, characterized in that the microspheres or microparticles have a mean diameter of from 5 to 150 $\mu$m, and preferably from 20 to 80

12. Implant according to Claim 3, characterized in that the microspheres or microparticles have a mean diameter of from 5 to 150 $\mu$m, and preferably from 20 to 80

13. Implant according to Claim 2, characterized in that the microspheres or microparticles are bioresorbable within a period of 1 year to 3 years.

14. Implant according to Claim 3, characterized in that the microspheres or microparticles are bioresorbable within a period of 1 year to 3 years.

15. Implant according to Claim 4, characterized in that the microspheres or microparticles are bioresorbable within a period of 1 year to 3 years.

16. Implant according to Claim 2, characterized in that said polymer is a poly acid chosen from poly-L-lactic acid, poly-D-lactic acid and mixtures thereof.

17. Implant according to Claim 3, characterized in that said polymer is a poly acid chosen from poly-L-lactic acid, poly-D-lactic acid and mixtures thereof.

18. Implant according to Claim 4, characterized in that said polymer is a poly acid chosen from poly-L-lactic acid, poly-D-lactic acid and mixtures thereof.

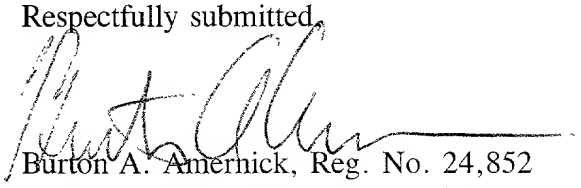
19. Implant according to Claim 5, characterized in that said polymer is a poly acid chosen from poly-L-lactic acid, poly-D-lactic acid and mixtures thereof.

20. Implant according to Claim 2, characterized in that the gel includes mainly gelling agent, carboxymethylcellulose (CMC) or hydroxypropylmethylcellulose (HPMC) concentration by weight of 0.1 to 7.5%, and preferably from 0.1 to 5.0%.

Remarks

The claims have been amended to eliminate multiple dependency and to improve format. None of these amendments is believed to involve any new matter. Accordingly is respectfully requested that the foregoing amendments be entered, that the application a amended receive an examination on the merits, and that the claims as now presented rec an early allowance.

Respectfully submitted,



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# IMPLANT FOR SUBCUTANEOUS OR INTRADERMAL INJECTION

The present invention relates to an implant for subcutaneous or intradermal injection, intended to be used in humans in reparative or plastic surgery and in esthetic dermatology, for filling wrinkles, fine lines, skin cracks, acne scars and other scars, as well as in dentistry for filling the gums.

Up until now, a number of products have been used for this purpose. Each product has advantages and disadvantages.

Silicone gel (or silicone oil) is easy to use. However, the migration of droplets of silicone into the tissues situated below the point of injection, by simple gravity, has been observed after injection. Silicone is frequently the cause of chronic inflammation, of formation of granulomas, and even of tardive allergic reactions. Silicone is not biodegradable, and it is often found in the liver.

Teflon paste is a suspension of polytetrafluoroethylene particles (diameter 10 to 100 µm) in glycerine. This product, in numerous cases, caused severe and chronic serous infections and had to be removed after a few months from dermal and subdermal tissues for most patients. It has also been proved that small polytetrafluoroethylene particles were found in the liver.

Collagen suspensions have been very widely used in the last ten years. The results have however been quite disappointing since collagen is resorbed within 1 to 3 months. Allergic reactions are also noted in about 2% of patients. Finally, it should be noted that collagen is of bovine origin.

Biological samples from the patient himself: the idea was certainly interesting, but clinical experience has shown the failure of the reimplantation of the fatty cells, which are absorbed and disappear within a few weeks.

Another system consisted in adding plasma from the patient to a collagen gelatin of bovine and porcine origin. The results are even more disappointing, and the

product is of animal origin.

Hyaluronate gels provided a good alternative by virtue of their biocompatibility and their lack of toxicity. They are moreover widely used in eye surgery. However, their rapid bioresorbability (maximum 2 months) makes them ineffective for use in plastic surgery.

Bioplastics are polymerized silicone particles (diameter 70 to 140 µm) dispersed in polyvinyl-pyrrolidone. The product had to be withdrawn given the chronic inflammation and the rejection reactions caused by it.

Polymethyl methacrylate (PMMA) microspheres having a diameter of 20 to 40 µm in suspension either in a solution of gelatin or in a solution of collagen. PMMA is not biodegradable, but not enough time has elapsed in order to know what this implant gives after 5 or 6 years. Moreover, the vector remains a solution of collagen of bovine origin, with the problems of allergy which are known for it.

The aim of the invention is to overcome the disadvantages of known products.

The invention uses microspheres or microparticles consisting of a neutral polymer chosen for its innocuousness and which is already widely used by the pharmaceutical industry either by the oral route or by the parenteral route.

The implant according to the invention combines ease of use without prior manipulations, syringeability of the product, resorbability over a controlled time of the polymer as well as of the vector gel, and absence of allergenicity of the product, which makes any preliminary test unnecessary.

The microspheres or microparticles should have a controlled bioresorbability offering a resorbability time of between 1 and 3 years. This means that the polymer will be degraded, after injection in situ, into low molecular-weight compounds which will be eliminated from the body by natural processes. In no case does a non resorbable implant appear to be desirable. It is still

foreign body placed in a living tissue.

The microspheres or microparticles are suspended in a gel. They should have a diameter greater than 5 µm and preferably greater than 20 µm, so as not to be absorbed by the macrophages. They should have a diameter of less than 150 µm, and preferably less than 40 µm, so that, on the one hand, they can be injected by a fine needle and, on the other hand, they do not create a granular mass under the finger.

Two families of polymers essentially meet the preceding definition: the polycaprolactones (and in particular the poly-ε-caprolactones), as well as the polylactides (polylactic acids or PLA), the polyglycolides (polyglycolic acids or PGA) and their copolymers (polylactic-co-glycolic acids or PLAGA).

Given the numerous studies already carried out and the good knowledge of the products, in particular as regards the manufacture of microspheres and resorbability, it appears advantageous to use a mixture of polylactic acid (PLA) and polylactic-co-glycolic acid (PLAGA). The proportions of each of these two acids make it possible to determine the persistence of the product.

Numerous trials have also led to a preference for a polymer consisting of a poly-L-lactic acid (crystalline), a poly-D-lactic acid (amorphous), or a mixture of these two acids. Its molecular mass, calculated by viscometry, is advantageously between 70,000 and 175,000 Dalton, and preferably between 120,000 and 170,000 Dalton, an intrinsic viscosity of between 3 and 4 dl/g, and preferably between 3.35 and 3.65 dl/g, a specific rotation of between -150 and -160°, a melting point of between 178.0 and 190.1°C, a heat of fusion of between 85.0 J/g and 90.0 J/g, a quantity of residual solvents < 0.01% and a proportion of residual monomer (lactic acid) < 0.1%. Such a product is available from PURAC BIOCHEM in Gorinchem (The Netherlands).

Bioresorbable synthetic polymers have been studied for about 15 years under the direction of Michel VERT, Director of Research at C.N.R.S. The first clinical

uses of PLAs started in 1981 for various indications in facial traumatology. The use of lactic acid polymers has become systematic in the context of bioresorbable surgical implants. PLAs now have diverse and wide medical applications (bone surgery, maxillo-facial surgery, controlled-release pharmacological formulations: implants, microspheres, nanospheres, vaccines).

The degradation of lactic acid and/or glycolic acid polymers in biological medium occurs exclusively by a chemical mechanism of nonspecific hydrolysis. The products of this hydrolysis are then metabolized and then eliminated by the human body. Chemical hydrolysis of the polymer is complete; the more pronounced its amorphous character and the lower its molecular mass, the more rapidly it occurs. Thus, the resorbability time may be adjusted by acting on the composition of the mixture and/or on the molecular mass of the polymer(s). The biocompatibility of the PLA and PLAGA polymers makes them excellent supports for cellular growth and tissue regeneration.

The microspheres or microparticles are included in a gel. This gel, which is used as vector to maintain the microspheres or microparticles in a homogeneous suspension, is resorbable within approximately 2 months, which corresponds to the time necessary for the creation of fibroses around the microspheres or microparticles. It consists mainly of water for injection and a gelling agent authorized in injection: cellulose derivatives, and more particularly carboxymethylcellulose (CMC) at a concentration by mass of 0.1 to 7.5%, and preferably from 0.1 to 5.0%. It is also possible to use hydroxypropyl-methylcellulose (HPMC) which is commonly used in intra-ocular injection in the context of cataract operations. It is also possible to use a synthetic hyaluronic acid, which is used for intraocular injections and subcutaneous injections. It is also possible to use lactic acid esters, caproic acid esters and the like.

The good dispersion of the microspheres or microparticles and the homogeneity of the gel will be

provided by the use of a surfactant chosen for its innocuousness and its authorized subcutaneous and intradermal use. Polyoxyethylene sorbitan monooleate (marketed under the name Tween 80) or pluronic acid will be used.

The product may be provided in ready-for-use prefilled sterile syringes, provided with a needle, or in vials of sterile suspension. It may also be provided in a vial containing a freeze-dried product accompanied by an ampule of sterile water (water for injection), or in a two-compartment prefilled syringe, one containing the freeze-dried product of microspheres or microparticles the other containing water for injection.

The implant does not require a test of allergenicity. It does not contain any product of animal origin.

The protocol for the manufacture of the implant is described below, in the case of a ready-for-use suspension of microspheres.

A. Preparation of microspheres of lactic acid polymer. The conventional solvent evaporation technique, or the so-called controlled precipitation technique or any other technique which makes it possible to obtain microspheres of the desired size is used.

B. Preparation of a gel of sufficient viscosity to maintain the microspheres in suspension. This viscosity will be adjusted depending on the size of the microspheres and the proportion of microspheres dispersed in the gel. This proportion will be from 50 to 300 g/l, and preferably from 60 to 200 g/l.

C. Distribution of the gel into syringes or into vials, in a controlled atmosphere (class $10^4$).

D. Sterilization of the vials or syringes, or use of a process which makes the finished product suitable for injection by the subcutaneous route.

The manufacturing protocol is described below in the case of freeze-dried PLA microparticles, whether this is the L polymer, the D polymer or a mixture thereof.

A. Cryogrinding of the PLA under gaseous nitrogen

filtered at 0.22 µm, at a temperature of less than -80°C, on a 100-µm screening grid.

B. Sieving of the microparticles on a 100-µm stainless steel sieve.

C. Preparation of the freeze-drying medium including the dissolution, with stirring, of CMC (gelling agent), of apyrogenic mannitol (cryoprotecting agent), and of polysorbate (surfactant) in water for injection, filtration at 0.22 µm of the solution obtained under gaseous nitrogen filtered at 0.22 µm, and sterilization in an autoclave for 20 minutes at 121.5°C.

D. Distribution of the microparticles at a rate of 100 mg per vial of 4 ml nominal capacity.

E. Distribution of the freeze-drying medium at a rate of 1.05 ± 0.05 g into the vials already containing the polylactic acid microparticles.

F. Dispersion of the microparticles in the freeze-drying medium by an ultrasound dispersion system in order to obtain a homogeneous suspension.

G. Prestoppering of the bottles using pillar stoppers (specific for freeze-drying), rapid freezing below -70°C, storage of the frozen vials below -40°C, and finally freeze-drying and automatic stoppering of the vials.

H. Fitting of capsules and examination of the vials, before sterilization by $\gamma$ irradiation.

Of course, it is possible to combine the procedures described above, for example in order to obtain a suspension of microparticles ready for use, or a freeze-dried product of microspheres, the microparticles or the microspheres consisting of any of the above-mentioned polymers and mixtures thereof.

**EXAMPLE 1**

2 g of PLA are dissolved in 20 ml of an organic solvent (ethyl acetate). This solution is dispersed in 100 ml of water containing 5 g of polyoxyethylene sorbitan monooleate. Moderate vortex stirring is maintained until evaporation of the solvent and formation of microspheres having a mean diameter of 40 µm. The micro-

spheres formed are recovered by sedimentation, filtration and drying. They are then included in a gel consisting of water and CMC (0.5% by mass). After moderate stirring, the distribution is carried out.

**EXAMPLE 2**

2 g of PLA are dissolved in 20 ml of an organic solvent (methylene chloride). This solution is dispersed in 100 ml of water containing 5 g of polyoxyethylene sorbitan monooleate. Moderate vortex stirring is maintained until evaporation of the solvent and formation of microspheres having a mean diameter of 80 µm. The microspheres formed are recovered by sedimentation, filtration and drying. They are then included in a gel consisting of water and CMC (0.5% by mass). After moderate stirring, the distribution is carried out.

**EXAMPLE 3**

2 g of PLA are dissolved in 20 ml of an organic solvent (chloroform). This solution is dispersed in 100 ml of water containing 5 g of polyoxyethylene sorbitan monooleate. Moderate vortex stirring is maintained until evaporation of the solvent and formation of microspheres having a mean diameter of 50 µm. The microspheres formed are recovered by sedimentation, filtration and drying. They are then included in a gel consisting of water and HPMC (1% by mass). After moderate stirring, the distribution is carried out.

**EXAMPLE 4**

600 g of polylactic acid are cryoground to a final particle size of between 20 and 100 µm, with a median at 40 µm. These microparticles are distributed at a rate of 100 mg per vial.

6.5 kg of freeze-drying medium are manufactured by dissolving 97.5 g of sodium CMC, 276.25 g of apyrogenic mannitol, and 6.5 g of polysorbate 80 in qs 6.5 liters of water for injection. This medium is distributed at a rate of 1 g per vial.

Trials were carried out on animals (hairless mice and New Zealand rabbits) with the products of Examples 1 to 4. The results are identical, and during the first two

months, and from the eighth day after the injection, the appearance of giant cells surrounding in a network the crystals of polylactic acid is observed followed by their transformation by creation of a fibrosis which reconstitutes the subcutaneous tissue.

Claims

1. Injectable implant for human administratio consisting of bioresorbable microspheres or micro particles in suspension in a gel.

2. Implant according to Claim 1, characterized i that the microspheres or microparticles consist of a least one polymer chosen from the poly-ε-caprolactones the lactic acid polymers, the glycolic acid polymers an the lactic co-glycolic acid polymers.

3. Implant according to either of Claims 1 and 2 characterized in that the proportion of microspheres o microparticles in the gel is from 50 to 300 g/l, an preferably from 60 to 200 g/l.

4. Implant according to one of the preceding claims characterized in that the microspheres or microparticle have a mean diameter of from 5 to 150 μm, and preferabl from 20 to 80 μm.

5. Implant according to one of the preceding claims, characterized in that the microspheres or microparticle are bioresorbable within a period of 1 year to 3 years.

6. Implant according to one of the preceding claims, characterized in that said polymer is a polylactic aci chosen from poly-L-lactic acid, poly-D-lactic acid an mixtures thereof.

7. Implant according to Claim 6, characterized i that the polylactic acid has a molecular mass of betwee 70,000 and 175,000 Dalton, and preferably between 120,00 and 170,000 Dalton, an intrinsic viscosity of between 3 and 4 dl/g, and preferably between 3.35 and 3.65 dl/g, a percentage of residual monomer <0.1% and a percentage of residual solvents <0.01%.

8. Implant according to one of the preceding claims, characterized in that the gel includes mainly, as gelling agent, carboxymethylcellulose (CMC) or hydroxypropyl-methylcellulose (HPMC) at a concentration by weight of 0.1 to 7.5%, and preferably from 0.1 to 5.0%.

9. Freeze-dried product obtained by freeze-drying a product according to one of the preceding claims, and capable of reconstituting an injectable implant by

addition of water for injection.

# DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare: My residence, post office address and citizenship are as stated below next to my n
am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names a
of the subject matter which is claimed and for which a patent is sought on the invention entitled
Implant for subcutaneous or intradermal injection the specification of which

(check one) ☐ is attached hereto.

☒ was filed on June 12, 1998 as Application Serial No. PCT/FR98/01241

and was amended on _____ (*if applicable*).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as a
amendment referred to above, and acknowledge a duty to disclose information which is material to the examination of this appli
CFR 1.56(a). I hereby claim priority benefits under 35 U.S.C. 119 based on any foreign application(s) for patent or inventor's c
below and have also identified below any foreign application for patent or inventor's certificate on the present invention,
application(s) on which priority is claimed.

| FOREIGN APPLICATION(S), IF ANY, REFERRED TO ABOVE | | | |
|---|---|---|---|
| COUNTRY | APPLICATION NUMBER | DAY, MONTH & YEAR FILED | PRIORIT |
| FRANCE | 97 07334 | 13 June 1997 | YES X |
| | | | YES ___ |
| | | | YES ___ |

I hereby claim benefit under 35 U.S.C. 120 of any U.S. application(s) listed below. If the subject matter of any claim(s) of this a
disclosed in the prior U.S. application(s) as required by paragraph one of 35 U.S.C. 112, I acknowledge a duty to disclose mate
as defined in 37 CFR 1.56(a) regarding occurrences between the filing date of the prior application(s) and the national or PC
filing date of this application:

| APPLICATION SERIAL NUMBER | DAY, MONTH & YEAR FILED | STATUS |
|---|---|---|
| PCT/FR98/01241 | 12 June 1998 | pending |
| | | |

I hereby appoint Elliott I. Pollock, RN (Registration No.) 16,906; George VandeSande, RN 17,276; Robert R. Priddy, RN 20
Amernick RN 24,852; Stanley B. Green, RN 24,351, Richard Wiener, RN 18,741; Townsend M. Belser, Jr., RN 22,956; Morris
Charles E. Snee, III, RN 26,610; Martin Abramson, RN 25,787; Dean E. Carlson, RN 18,537; and George Pettit, RN 27,369, m
full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Tr
connected therewith.

Address all communications to POLLOCK, VANDE SANDE & AMERNICK - P.O. Box 19088 WASHINGTC

All statements made herein of my own knowledge are true. All statements made on information and belief are believed t
statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonmer
18 U.S.C. 1001 and may jeopardize the validity of the application or any patent issuing thereon.

Note: Please sign one full given name and your surname, using initials where appropriate for other names. It is important
consistent throughout the application papers. Signing of an application more than five weeks prior to filing or an undat
not acceptable to the Patent and Trademark Office except for receiving an initial filing date.

100

1. Full name of inventor Jérôme ASIUS Date: 19/
Inventor's signature Jérôme ASIUS
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FR
Citizenship France
Post Office Address the same as above

200

2. Full name of inventor Hatem FESSI Date: 20/0
Inventor's signature Hatem Fessi
Residence 40, rue d'Aubigny - F 69003 LYON (France) FRX
Citizenship France
Post Office Address the same as above

# DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare: My residence, post office address and citizenship are as stated below next to my r
am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names a
of the subject matter which is claimed and for which a patent is sought on the invention entitled
Implant for subcutaneous or intradermal injection the specification of which

(check one) ☐ is attached hereto.

☒ was filed on June 12, 1998 as Application Serial No. PCT/FR98/01241

and was amended on _____ (*if applicable*)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as a
amendment referred to above, and acknowledge a duty to disclose information which is material to the examination of this appli
CFR 1.56(a). I hereby claim priority benefits under 35 U.S.C. 119 based on any foreign application(s) for patent or inventor's
below and have also identified below any foreign application for patent or inventor's certificate on the present invention,
application(s) on which priority is claimed.

| FOREIGN APPLICATION(S), IF ANY, REFERRED TO ABOVE | | | |
|---|---|---|---|
| COUNTRY | APPLICATION NUMBER | DAY, MONTH & YEAR FILED | PRIORIT |
| FRANCE | 97 07334 | 13 June 1997 | YES X |
| | | | YES ___ |
| | | | YES ___ |

I hereby claim benefit under 35 U.S.C. 120 of any U.S. application(s) listed below. If the subject matter of any claim(s) of this a
disclosed in the prior U.S. application(s) as required by paragraph one of 35 U.S.C. 112, I acknowledge a duty to disclose mate
as defined in 37 CFR 1.56(a) regarding occurrences between the filing date of the prior application(s) and the national or PC
filing date of this application:

| APPLICATION SERIAL NUMBER | DAY, MONTH & YEAR FILED | STATUS |
|---|---|---|
| PCT/FR98/01241 | 12 June 1998 | pending |
| | | |

I hereby appoint Elliott I. Pollock, RN (Registration No.) 16,906; George VandeSande, RN 17,276; Robert R. Priddy, RN 2(
Amernick RN 24,852; Stanley B. Green, RN 24,351; Richard Wiener, RN 18,741; Townsend M. Belser, Jr., RN 22,956; Morris
Charles E. Snee, III, RN 26,610; Martin Abramson, RN 25,787; Dean E. Carlson, RN 18,537; and George Pettit, RN 27,369, n
full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and T
connected therewith.

Address all communications to POLLOCK, VANDE SANDE & AMERNICK - P.O. Box 19088 WASHINGT(

All statements made herein of my own knowledge are true. All statements made on information and belief are believed t
statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonme
18 U.S.C. 1001 and may jeopardize the validity of the application or any patent issuing thereon.

Note: Please sign one full given name and your surname, using initials where appropriate for other names. It is important
consistent throughout the application papers. Signing of an application more than five weeks prior to filing or an unda
not acceptable to the Patent and Trademark Office except for receiving an initial filing date.

300 3 Full name of inventor Franck GOUCHET Date: 21/

Inventor's signature Franck Gouchet

Residence 8, allée des Chasseurs - F 45450 DONNERY (France)

Citizenship France FRX

Post Office Address the same as above

400 4 Full name of inventor Bénédicte LAGLENNE Date: 18/

Inventor's signature Bénédicte Laglenne

Residence Les Campagnes - Le Mas Neuf, Route de Saint Aunes - F 34130 MAUGUIO (Fra FR

Citizenship France

Post Office Address the same as above

# DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare: My residence, post office address and citizenship are as stated below next to my r
am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names a
of the subject matter which is claimed and for which a patent is sought on the invention entitled
Implant for subcutaneous or intradermal injection the specification of which

(check one) ☐ is attached hereto.

☒ was filed on June 12, 1998 as Application Serial No. PCT/FR98/01241

and was amended on _____ (*if applicable*).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as a
amendment referred to above, and acknowledge a duty to disclose information which is material to the examination of this appli
CFR 1.56(a). I hereby claim priority benefits under 35 U.S.C. 119 based on any foreign application(s) for patent or inventor's
below and have also identified below any foreign application for patent or inventor's certificate on the present invention,
application(s) on which priority is claimed.

| FOREIGN APPLICATION(S), IF ANY, REFERRED TO ABOVE | | | |
|---|---|---|---|
| COUNTRY | APPLICATION NUMBER | DAY, MONTH & YEAR FILED | PRIORIT |
| FRANCE | 97 07334 | 13 June 1997 | YES X |
| | | | YES ___ |
| | | | YES ___ |

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Full name of inventor Elisabeth LAUGIER-LAGLENNE Date: 27

Inventor's signature E. Laugier-Laglenne

Residence 25-27, rue Tronchet - F 75008 PARIS FRX

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2. Full name of inventor _____ Date: ___

Inventor's signature _____

Residence _____

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